CHAPTER 4

TOXICITY ASSESSMENT

4.1 PRINCIPLES OF ROUTE-TO-ROUTE EXTRAPOLATION

Dermal contact with contaminants can result in direct toxicity at the site of application and/or contribute to systemic toxicity via percutaneous absorption. The issue of direct toxicity is addressed in Section 4.4. Ideally, a route-specific (i.e., dermal) toxicity factor would not only consider portal-of-entry effects (i.e., direct toxicity) but would also provide dosimetry information on the dose-response relationship for systemic effects via percutaneous absorption.

In the absence of dermal toxicity factors, EPA has devised a simplified paradigm for making route-to-route (oral-to-dermal) extrapolations for systemic effects. This process is outlined in Appendix A of RAGS/HHEM (U.S. EPA, 1989). Primarily, it accounts for the fact that most oral reference doses (RfDs) and slope factors are expressed as the amount of substance administered per unit time and body weight, whereas exposure estimates for the dermal pathway are expressed as absorbed dose. The process utilizes the dose-response relationship obtained from oral administration studies and makes an adjustment for absorption efficiency to represent the toxicity factor in terms of absorbed dose.

This approach is subject to a number of factors that might compromise the applicability of an oral toxicity factor for dermal exposure assessment. The estimation of oral absorption efficiency, to adjust the toxicity factor from administered to absorbed dose, introduces uncertainty. Part of this uncertainty relates to distinctions between the terms "absorption" and "bioavailability." Typically, the term absorption refers to the "disappearance of chemical from the gastrointestinal lumen," while oral bioavailability is defined as the "rate and amount of chemical that reaches the systemic circulation unchanged." That is, bioavailability accounts for both absorption and pre-systemic metabolism. Although pre-systemic metabolism includes both gut wall and liver metabolism, for the most part it is liver metabolism or liver "first pass" effect that plays the major role.

In the absence of metabolic activation or detoxification, toxicity adjustment should be based on bioavailability rather than absorption because the dermal pathway purports to estimate the amount of parent compound entering the systemic circulation. Metabolism in the gut wall and skin can serve to complicate this otherwise simplified adjustment process. Simple adjustment of the oral toxicity factor, based on oral absorption efficiency, does not account for metabolic by-products that might occur in the gut wall but not the skin, or conversely in the skin, but not the gut wall.

More importantly the oral administered dose experiences the liver "first pass"effect. The efficiency of "first pass" metabolism and whether this is an activating or detoxifying process determines the nature of the impact this effect has on route-to-route extrapolations. One example is a compound that exhibits poor oral systemic bioavailability due to a prominent "first pass" effect which creates a highly toxic metabolite. The adjusted dermal toxicity factor may overestimate the true dose-response relationship because it would be based upon the amount of parent compound in the systemic circulation rather than on the toxic metabolite. Additionally, percutaneous absorption may not generate the toxic metabolite to the same rate and extent as the gastrointestinal route.

Toxicity is a function of contaminant concentration at critical sites-of-action. Absorption rate, as well as extent of absorption, determines contaminant concentration at a site-of-action. Differences in the anatomic barriers of the gastrointestinal tract and the skin can affect rate as well as the extent of absorption; therefore, the route of exposure may have significant dose-rate effects at the site-of-action.

4.2 ADJUSTMENT OF TOXICITY FACTORS

Methodologies for evaluating percutaneous absorption, as described in *DEA* give rise to an estimation of absorbed dose. However, Integrated Risk Information System (IRIS)-verified indices of toxicity (e.g., RfDs, slope factors) are typically based on administered dose. Therefore, to characterize risk from the dermal exposure pathway, adjustment of the oral toxicity factor to represent an absorbed rather than administered dose is necessary. This adjustment accounts for the absorption efficiency in the "critical study," which forms the basis of the RfD. For example, in the case where oral absorption in the critical study is essentially complete (i.e., 100%), the absorbed dose is equivalent to the administered dose, and therefore no toxicity adjustment is necessary. When gastrointestinal absorption of a chemical in the critical study is poor (e.g., 1%), the absorbed dose is much smaller than the administered dose; thus, toxicity factors based on absorbed dose should be adjusted to account for the difference in the absorbed dose relative to the administered dose.

In effect, the magnitude of toxicity factor adjustment is inversely proportional to the absorption fraction in the critical study. That is, when absorption efficiency in the critical study is high, the absorbed dose approaches the administered dose resulting in little difference in a toxicity factor derived from either the absorbed or administered dose. As absorption efficiency in the critical study decreases, the difference between the absorbed dose and administered dose increases. At some point, a toxicity factor based on absorbed rather than administered dose should account for this difference in dose. In practice, an adjustment in oral toxicity factor (to account for "absorbed dose" in the dermal exposure pathway) is recommended when the following conditions are met: (1) the toxicity value derived from the critical study is based on an administered dose (e.g., delivery in diet or by gavage) in its study design; (2) a scientifically defensible database demonstrates that the gastrointestinal (GI) absorption of the chemical in question, from a medium (e.g., water, feed) similar to the one employed in the critical study, is significantly

less than 100% (e.g., <50%). A cutoff of 50% GI absorption is recommended to reflect the intrinsic variability in the analysis of absorption studies. Thus, this cutoff level obviates the need to make comparatively small adjustments in the toxicity value that would otherwise impart on the process a level of accuracy that is not supported by the scientific literature.

If these conditions are not met, a default value of complete (i.e., 100%) oral absorption may be assumed, thereby eliminating the need for oral toxicity-value adjustment. The Uncertainty Analysis could note that employing the oral absorption default value may result in underestimating risk, the magnitude of which being inversely proportional to the true oral absorption of the chemical in question.

The recommended GI absorption values (ABS_{GI}) for those compounds with chemical-specific dermal absorption factors from soil are presented in Exhibit 4-1. For those organic chemicals that do not appear on the table, the recommendation is to assume a 100% ABS_{GI} value, based on review of literature, indicating that organic chemicals are generally well absorbed (>50%) across the GI tract. Absorption data for inorganics are also provided in Exhibit 4-1, indicating a wide range of absorption values for inorganics. Despite the wide range of absorption values for inorganics, the recommendation is to assume a 100% ABS_{GI} value for inorganics that do not appear in this table. This assumption may contribute to an underestimation of risk for those inorganics that are actually poorly absorbed. The extent of this underestimation is inversely proportional to the actual GI absorption. These criteria are recommended for the adjustment of toxicity values for the assessment of both soil and water contact.

Equation 4.1 indicates that as the ABS_{GI} value decreases, the greater is the contribution of the dermal pathway to overall risk relative to the ingestion pathway. Therefore, the ABS_{GI} can greatly influence the comparative importance of the dermal pathway in a risk assessment.

4.3 CALCULATION OF ABSORBED TOXICITY VALUES

Once the criteria for adjustment have been met and a specific ABS_{GI} value has been identified, a

Impact of Oral Absorption Efficiency on the Ratio of Dermal to Ingestion Risk

$$\frac{\text{Dermal Risk}}{\text{Ingestion Risk}} \propto \frac{1}{ABS_{GI}} \qquad (4.1)$$

where:

Parameter		Definition (units)	Default Value
ABS_{GI}	=	Fraction of contaminant absorbed in gastrointestinal tract (dimensionless) in the critical toxicity study	Chemical-specific, see Exhibit 4-1 and Appendix B

toxicity factor that reflects the absorbed dose can be calculated from the oral toxicity values as presented in Equations 4.2 and 4.3.

The RfD_{ABS} and SF_{ABS} should be used in the calculation of dermal risk, as described in Chapter 5.

4.4 DIRECT TOXICITY

The discussion in Section 4.2 on toxicity factor adjustment is based on the evaluation of chronic systemic effects resulting from GI absorption. Chapter 3 of this document provides a methodology for estimating a systemically absorbed dose secondary to dermal contact with chemicals in water and soil.

However, dermal contact with a chemical may also result in direct dermal toxicity, such as allergic contact dermatitis, urticarial reactions, chemical irritation, and skin cancer. EPA recognizes that the dose-response relationship for the portal-of-entry effects in the skin are likely to be independent of any associated systemic toxicity exhibited by a particular chemical. However, at this time, chemical specific dermal toxicity factors are not available. Therefore, this dermal risk assessment guidance does not address potential dermal toxicity associated with direct contact. The dermal risk assessment methodology in this guidance may be revised to incorporate additional information on portal-of-entry effects as it becomes available.

Derivation of Cancer Slope Factor based on Absorbed Dose

$$SF_{ABS} = \frac{SF_O}{ABS_{GI}} \qquad (4.2)$$

where:

Parameter		Definition (units)	Default Value
SF_{ABS}	=	Absorbed slope factor	Chemical-specific, See Exhibit 4-1
SF_O	=	Oral slope factor $(mg/kg\text{-}day)^{-1}$	Chemical-specific
ABS_{GI}	=	Fraction of contaminant absorbed in gastrointestinal tract (dimensionless) in the critical toxicity study.	Chemical-specific, see Exhibit 4-1 and Appendix B

Derivation of Reference Dose based on Absorbed Dose

$$RfD_{ABS} = RfD_{O} \times ABS_{GI} \quad (4.3)$$

where:

Parameter		Definition (units)	Default Value
RfD_{ABS}	=	Absorbed reference dose (mg/kg-day)	Chemical-specific, see Exhibit 4-1
RfD_{O}	=	Reference dose oral (mg/kg-day)	Chemical-specific
ABS_{GI}	=	Fraction of contaminant absorbed in gastrointestinal tract (dimensionless) in the	Chemical-specific, see Exhibit 4-1 and Appendix B

EXHIBIT 4-1

SUMMARY OF GASTROINTESTINAL ABSORPTION EFFICIENCIES AND RECOMMENDATIONS FOR ADJUSTMENT OF TOXICITY FACTORS FOR SPECIFIC COMPOUNDS

Compound	GI Absorption				IRIS Critical Toxicity Study			Adjust?
	Ref[1]	Species	Dosing Regimen	% Absorbed ABS_{GI}	Species	Dosing Regimen	Toxicity Factor	
Organics								
Chlordane	Ewing, 1985 Ohno, 1986	Rats	assume aqueous gavage	80%	Mice	diet	SF	No
					Mice	inhalation	RfD	
2,4-Dichlorophenoxyacetic acid (2,4-D)	Knopp, 1992 Pelletier, 1989	Rats	assume aqueous gavage	>90%	Rats	diet	RfD	No
DDT	Keller, 1980	Rats	vegetable oil	70-90%	Rats	dissolved in oil, mixed with diet	RfD	No
Pentachlorophenol	Korte, 1978	Rats	diet	76%	Rats	diet	RfD	No
	Meerman, 1983	Rats	water	100%				
Polychlorinated biphenyls (PCBs)	Albro, 1972	Rats	squalene	96%	Rats	diet	SF	No
	Muhlebach, 1981	Rats	emulsion	80%				
	Tanabe, 1981	Rats	corn oil	81%				

EXHIBIT 4-1

SUMMARY OF GASTROINTESTINAL ABSORPTION EFFICIENCIES AND RECOMMENDATIONS FOR ADJUSTMENT OF TOXICITY FACTORS FOR SPECIFIC COMPOUNDS (continued)

Compound	GI Absorption				IRIS Critical Toxicity Study			Adjust?
	Ref[1]	Species	Dosing Regimen	% Absorbed ABS_{GI}	Species	Dosing Regimen	Toxicity Factor	
Polycyclic aromatic hydrocarbons(PAHs)	Chang, 1943	Rats	starch solution	58%	Mice	diet	SF	No
	Hecht, 1979	Rats	diet	89%				
TCDD	Fries, 1975	Rats	diet	50-60%	under review			No
	Piper, 1973	Rats	diet	70%				
	Rose, 1976	Rats	corn oil	70-83%				
Other Dioxins/ Dibenzofurans	ATSDR, 1994a	multiple studies		>50%	under review			No
All other organic compounds	multiple references			generally >50%	multiple studies		RfD or SF	No
Inorganics								
Antimony	Waitz, 1965	Rats	water	15%	Rat	water	RfD	Yes
Arsenic (arsenite)	Bettley, 1975	Human	assume aqueous	95%	Human	water	SF	No
Barium	Cuddihy and Griffith, 1972 Taylor, 1962	Dog	water	7%	Human	water	RfD	Yes
Beryllium	Reeves, 1965	Rats	water	0.7%	Rat	water	RfD	Yes
Cadmium	IRIS, 1999	Human	diet	2.5%	Human	diet and water	RfD	Yes

EXHIBIT 4-1

SUMMARY OF GASTROINTESTINAL ABSORPTION EFFICIENCIES AND RECOMMENDATIONS FOR ADJUSTMENT OF TOXICITY FACTORS FOR SPECIFIC COMPOUNDS (continued)

Compound	GI Absorption				IRIS Critical Toxicity Study			Adjust?
	Ref[1]	Species	Dosing Regimen	% Absorbed ABS_{GI}	Species	Dosing Regimen	Toxicity Factor	
		Human	water	5%				Yes
Chromium (III)	Donaldson and Barreras, 1996 Keim, 1987	Rats	diet/water	1.3%	Rat	diet	RfD	Yes
Chromium (VI)	Donaldson and Barreras, 1996 MacKenzie, 1959 Sayato, 1980	Rats	water	2.5%	Rat	water	RfD	Yes
Cyanate	Farooqui and Ahmed, 1982	Rats	assume aqueous	>47%	Rat	diet	RfD	No
Manganese	Davidsson, 1989 IRIS, 1999 Ruoff, 1995	Human	diet/water	4%	Human	diet/water	RfD	Yes
Mercuric chloride (other soluble salts)	IRIS, 1999	Rats	water	7%	Rat	oral gavage in water; 2X/week	RfD	Yes
Insoluble or metallic mercury	ATSDR, 1994b	Human	acute inhalation of Hg vapor	74-80%	Human	Inhalation	RfC	No
Methyl mercury	Aberg, 1969	Human	aqueous	95%	Human	diet	RfD	No
Nickel	Elakhovskaya, 1972	Human	diet/water	4%	Rat	diet	RfD	Yes

EXHIBIT 4-1

SUMMARY OF GASTROINTESTINAL ABSORPTION EFFICIENCIES AND RECOMMENDATIONS FOR ADJUSTMENT OF TOXICITY FACTORS FOR SPECIFIC COMPOUNDS (continued)

Compound	GI Absorption				IRIS Critical Toxicity Study			Adjust?
	Ref[1]	Species	Dosing Regimen	% Absorbed ABS_{GI}	Species	Dosing Regimen	Toxicity Factor	
Selenium	Young, 1982	Human	diet	30-80%	Human	diet	RfD	No
Silver	Furchner, 1968 IRIS, 1999	Dogs	aqueous	4%	Human	i.v. dose	RfD (based on estimated oral dose)	Yes
Thallium	Lie, 1960	Rats	aqueous	100%	Rat	water gavage	RfD	No
Vanadium	Conklin, 1982	Rats	gavage	2.6%	Rat	diet as V_2O_5	RfD	Yes
Zinc	ATSDR, 1994c	Human	diet	highly variable	Human	diet supplement	RfD	No

[1] Literature references are listed here by first author. Complete citations are provided in Reference Section.